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LEAVITT, MARIA GOMEZ				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/573,813

Applicant(s)

WADA ET AL.

Examiner

MARIA LEAVITT

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7, 15, 16, 18, 19, 22 and 41-75 is/are pending in the application.
- 4a) Of the above claim(s) 22 and 46-75 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7, 15, 16, 18, 19 and 41-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claims 7, 15, 16, 18, 19, 22, 41-75 are currently pending. Claims 7, 15, 18, 19 and 22 have been amended, and claims 22 and 46-75 have been withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim by Applicant's amendment filed on 12-23-2009.
3. Accordingly, claims 7, 15, 16, 18, 19 and 41-45 are currently under examination to which the following grounds of rejection are applicable.

Response to arguments

Objections/ Rejections withdrawn in response to Applicants' arguments or amendments

Claim Objections

In view of Applicants' amendment of the Title of the Invention to delete the phrase in parenthesis, objection to the title has been withdrawn.

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants' amendment claims 18 and 19, rejection of claims 18 and 19 under 35 U.S.C. § 112, second paragraph, has been withdrawn.

Applicants' arguments are moot in view of the withdrawn rejection.

Rejections maintained in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 103

Claims 7, 15, 16, 18, 42 and 44 remain rejected under 35 USC 103 as being unpatentable over Zhou et al., (Jan. 2003, Applied and Environmental Microbiology, pp. 399-407, or record) in view of Yang et al., (1999, Metabolic Engineering, pp. 141-152, of record) as evidenced by Bunch et al., (Microbiology 1997, pp.187-195, of record) and further in view of Shaw et al., (1975, J. Bacteriology, pp. 1047-1975).

Reply to applicants' arguments as they relate to rejection of claims 7, 15, 16, 18, 42 and 44 under 35 USC § 103

At pages 11-14 of the remarks filed on 12-23-2009, Applicants essentially argue that: 1) Zhou discloses production of D-lactic acid by disruption of *pflB*, *adhE*, *frdABCD* and *ackA* genes in *E. coli* to produce a strain named SZ63, 2) Zhou does not teach a metabolically engineered *E. coli* W3110 wherein *E. coli* -derived NADH-dependent D-lactate dehydrogenase (*ldhA*) inherent in the microorganism is enhanced, 3) Zhou's SZ63 strain yielded 539 mM in 24 hours (Zhou, p. 403, Table 3), corresponding to 48.5 g/L in 24 hours, 4) in contrast, two strains of the claimed microorganisms produced 115.6 g/L in 48 hours and 113.5 g/L in 30 hours, respectively, a substantial increase (Specification, ¶[0184]), 4) Yang discloses that introducing *ldhA* gene with a plasmid leads to increased production of D-lactic acid, however, Yang's bacteria with increased *ldhA* also had increased production of pyruvate, formate, hydrogen, ethanol and acetate, 5) by product production of pyruvate, formate, hydrogen, ethanol and acetate in production of D-lactic acid are not desired requiring their removal, 6), "In contrast, the present inventors were able to achieve unexpected and surprising reductions in pyruvate by inactivating *pfl* while enhancing *ldhA*. Example 7, ¶[0149], Table 7. Disruption of *pfl* alone

(MG1655Apfl) resulted in the same level of pyruvic acid as the control (MG1655), however *pfl* deletion in combination with enhanced *ldhA* (MG1655Apfl/pGlyldhA) desirably and surprisingly reduced pyruvic acid”, 7) Shaw is relied upon for *E. coli* strains comprising L and D- membrane bound flavoproteins lactate dehydrogenases coupled to the respiratory chain, however, the data of the present application surprisingly demonstrate that the claimed gene disruption of *ldd* desirably reduced the accumulation of undesired products when *ldhA* was enhanced, 8) “given the large number of enzymes in the relevant biochemical pathways, together with the possibility for genetic modification of nearly any number of them simultaneously, the resulting number of combinations is so large that it would be practically impossible to try all such combinations. When no direction as to which of many possible choices is likely to be successful, an invention would not have been obvious to try” and 9), Bunch reported that *pfl*/*ldhA* double mutants cannot grow anaerobically on any sugar or alcohol even when supplemented with acetate, in contrast to single *ldhA* mutants which show no anaerobic growth defect (Bunch p. 191, right column, last paragraph). The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), the fact that Zhou et al., generates a SZ63 *E. coli* W3110 mutant for the production of D-lactic acid by deleting competing pathways by chromosomal inactivation of genes encoding fumarate reductase (*frdABCD*), alcohol/aldehyde dehydrogenase (*adhE*), pyruvate formate lyase (*pflB*) and acetate kinase gene (*ackA*) is not disputed. However, in nonpreferred embodiments Zhou et al., discloses inactivation of merely *pflB* to generate the SZ32 mutant able to exhibit increased production of D-lactic acid in relation to parental strain W3110, e.g. 49.23±1.26 vs. 30.69 ±2.49, respectively (page 402, Table 2). Moreover, the single

mutation eliminated production of competing pathways leading to production of formate, ethanol, and acetate in tube cultures containing 1% glucose (see Fig.1 for illustration of primary fermentation products and corresponding metabolic enzymes). Note that the pyruvate node represents the branch point between lactate dehydrogenase (LDH), which catalyzes the formation of lactate, and pyruvate formate lyase (*pflB*), which leads to the formation of formate and acetyl-CoA under anaerobic conditions. One of ordinary skill in the art would recognize that by deleting *pfl*, thus reducing or eliminating the routes leading to formation of formate and acetate, the pool of pyruvate would be increased and the flux from pyruvate could be shifted from the production routes of formate and acetyl-CoA to the production route of D- lactate with a reasonable expectation of success. Indeed, Zhou et al., states that “The distribution of carbon among these products is largely determined by the relative in vivo activities of D-lactate dehydrogenase (*ldhA* gene), pyruvate formate lyase (*pfl* gene), and phosphoenolpyruvate carboxylase (*ppc* gene)” (page 401, col. 2, last paragraph) clearly underlining the metabolic relevance of the pyruvate node. Note that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Regarding 2), in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). None of the references has to teach each and every claim limitation. If they did, this would have been anticipation and not an obviousness-type rejection. Yang et al., complements the teachings of

Zhou et al., by disclosing amplification of the lactate flux resulting from overexpression of fermentative lactate dehydrogenase (LDH) with a plasmid carrying the NADH-dependent D-lactate dehydrogenase (*ldhA*) gene. Therefore, Applicant's argument that Zhou fails to disclose the claimed enhanced activity of NADH-dependent D-lactate dehydrogenase (*ldhA*) in a microorganism is irrelevant.

Regarding 3) and 4) with respect to applicants' argument that, "Zhou's SZ63 strain yielded 539 mM in 24 hours (Zhou, p. 403, Table 3), corresponding to 48.5 g/L in 24 hours, two strains of the claimed microorganisms produced 115.6 g/L in 48 hours and 113.5 g/L in 30 hours, respectively, a substantial increase (Specification, ¶[0184])," is not found persuasive because it is noted that the features upon which applicant relies (i.e., , two strains of the claimed microorganisms produced 115.6 g/L in 48 hours and 113.5 g/L in 30 hours) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26USPQ2d 1057 (Fed. Cir. 1993). This is the case here. The claims do not recite the claimed microorganisms that produced 115.6 g/L in 48 hours and 113.5 g/L in 30 hours, i.e. MG1655ΔpflΔdld/pGAPldhA strain and MG1655ΔpflΔdld/pGAPldhA genome-inserted strain, respectively, taught at ¶ [0184] of the published application.

Regarding 5) and 6), the instant claims are product claims drawn to any microorganism wherein the inherent activity of the FAD-dependent *dld* inherent in the microorganism is reduced, activity of *pfl* is reduced and activity of a NADH-dependent *ldhA* obtained from *E. coli* and inherent in the microorganism is enhanced. Claim 22 further limits the microorganism to having either one of the *mdh* or *aspA* inherent activity decreased. Note that no functional

limitation is required for the claimed microorganism. All what is required in the claimed invention is the structure of the mutant microorganism. Applicants have not provided an example of a structural limitation that was not address, nor any structural limitations added by the contemplation of an intended use, e.g., D-lactic acid production. As stated in the paragraph above, the pyruvate node represents the branch point between lactate dehydrogenase (LDH), which catalyzes the formation of lactate, and pyruvate formate lyase (*pflB*). So if mutation of the *pfl* gene inherent in *E. coli* leads to enhanced production of D-lactic acid and overexpression of fermentative of NADH-dependent *ldhA* gene leads to enhanced production of D-lactic acid, the combination of a *pfl* deletion with enhanced *ldhA* should be reasonably expected to promote enhanced production of D-lactic acid in *E. coli* because both metabolic pathways represent competing branches for pyruvate (see Zhou et al., Fig.1 for illustration of primary fermentation products and corresponding metabolic enzymes). Accordingly, the motivation to combine the disclosure of Zhou and Yang would be to generate an engineered microorganism able to successfully redirect more carbon to the lactate dehydrogenase branch by eliminating enzymes that compete for pyruvate and thus enhancing pyruvate production which is a precursor in the formation of lactate. Indeed, Applicants have successfully demonstrated enhanced production of D-lactic acid in *E. coli* with a *pfl* deletion and enhanced *ldhA*, i.e. G1655ΔpflpGlyldhA, versus parental MG1655 (e.g., 52 g/L versus 95 g/L, Example 7, ¶[0149] of the published application, Table 7). Applicants are respectfully reminded of the case law, namely, that the "teaching, suggestion, motivation" test (the "TSM" test) which is often used to prove obviousness was revised somewhat in a recent Supreme Court decision. See *KSR International Co. v. Teleflex Inc.* et al., No. 04-1350, slip op. at 16 (S.Ct., April 30, 2007). This test, as applied in this case, was

determined to be too rigidly applied. The Supreme Court said: "There is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis. But when a court transforms the general principle into a rigid rule that limits the obviousness inquiry... it errs." The Federal Circuit erred by (1) looking only at the problem the patentee was trying to solve, (2) assuming that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem (3) concluding that a patent claim cannot be proved obvious by showing the combination of elements was "obvious to try," and (4) applying a rigid rule to prevent hindsight that denied fact finders "recourse to common sense." In its broadest sense, the KSR decision broadens the inquiry that must be made when proving an invention is obvious over prior art. Before this decision, when combining references, an Examiner must show a motivation by the person of skill in the art to combine the teachings of the different references. In the decision, the Supreme Court states that such a showing is not required, but only a "reason" to combine the teachings should be shown. This reason can be based upon logic, common sense, and/or the knowledge in the art. The Court stated that when familiar elements are combined according to known methods, the invention is likely to be obvious when it does no more than yield predictable results." KSR, slip op. at 12.

Regarding 7), note that the instant claims are product claims and do not recite any functional language. Therefore, Applicants' arguments at page 14 insofar as increased production of D-lactate and reduced production of undesired products resulting from the claimed invention that are entirely unexpected and nonobvious are not on point.

Regarding 8), the fact that metabolic engineering is a complex science is not disputed. However, it is well established in the art that advances in genetic engineering have enable

introduction of directed genetic changes through recombinant DNA technology and optimization of fermentation processes in part due to large physiological knowledge of fluxes through the different branches in the fermentative pathways in *E. coli* for the production of D-lactate (see Nielsen, 2001, *Appl Microbiol Biotechnol* pp. 263-268, Review). Thus the level of skill and knowledge in the art is such that one of ordinary skill would be able to routinely make and identify microorganism wherein the activity of the FAD-dependent *dld* inherent in the microorganism is reduced, activity of *pfl* is reduced and activity of a NADH-dependent *ldhA* obtained from *E. coli* in the microorganism is enhanced.

Regarding 9), the examiner notes that Bunch is merely cited as evidence to the plasmid pFB15, a multicopy vector taught Yang, carrying the *ldhA* gene under the control of the *ldhA* promoter. Bunch disclosure is not part of the claim rejection under 35 U.S.C. 103(a). As such, Applicant's arguments are not on point.

Claims 41, 43 and 45 remain rejected under 35 USC 103 as being unpatentable over Zhou et al., (Jan. 2003, *Applied and Environmental Microbiology*, pp. 399-407, of record) in view of Yang et al., (1999, *Metabolic Engineering*, pp. 141-152, of record) as evidenced by Bunch et al., (*Microbiology* 1997, pp.187-195, of record) and Shaw et al., (1975, *J. Bacteriology*, pp. 1047-1975) as applied to claims 7, 15, 16, 18, 42 and 44 above, and further in view of Courtright et al., (*J Bacteriol.* 1970, pp. 722-728, of record).

Reply to applicants' arguments as they relate to rejection of claims 41, 43 and 45 under 35 USC § 103

At pages 16-18 of the remarks filed on 12-23-2009, Applicants essentially argue that: 1) the reference of Zhou discloses deactivation of *frd* for reduced succinate whereas claims 41, 43 and 45 recited that *mdh* has been inactivated or decreased and not *frd*, 2), “As described in the present specification, a mutant obtained by disrupting *frd* in the strain MG1655ApflAdld (referred to “MG1655ApflAdldAfrd”) produces D-lactic acid in an amount of 71 g/L in 32 hours, and a strain according to the invention MG1655ApflAdldAmdh produces D-lactic acid in an amount of 89 g/L in 32 hours. Specification, ¶¶[0200] - [0201]” and 3), “as compared with the control MG1655ApflAdld, strains corresponding to that of Zhou (namely MG1655ApflAdldAfrd) would appear to inhibit the accumulation of D-lactic acid, while inhibiting the accumulation of succinic acid. On the other hand, the mutant of the of invention MG1655ApflAdldAmdh enhances the accumulation of D-lactic acid, while inhibiting the accumulation of succinic acid”. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1)-3), with respect to applicants' arguments that, " MG1655ApflAdldAmdh produces D-lactic acid in an amount of 89 g/L" and "MG1655ApflAdldAmdh enhances the accumulation of D-lactic acid, while inhibiting the accumulation of succinic acid" are not found persuasive because it is noted that the features upon which applicant relies (i.e., MG1655ApflAdldAmdh produces D-lactic acid in an amount of 89 g/L and MG1655ApflAdldAmdh enhances the accumulation of D-lactic acid, while inhibiting the accumulation of succinic acid) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26USPQ2d 1057 (Fed. Cir. 1993). This is the case

here. The claims do not recite the claimed “MG1655ApflAdIdAmdh enhances the accumulation of D-lactic acid, while inhibiting the accumulation of succinic acid”, taught at ¶ [0200] of the published application, for example.

Claim 18 and 19 remain rejected under 35 USC 103 as being unpatentable over Zhou et al., (Jan. 2003, Applied and Environmental Microbiology, pp. 399-407, of record) in view of Yang et al., (1999, Metabolic Engineering, pp. 141-152, of record) as evidenced by Bunch et al., (Microbiology 1997, pp.187-195, of record) and Shaw et al., (1975, J. Bacteriology, pp. 1047-1975) as applied to claims 7, 15, 16, 18, 42 and 44 above, and further in view of Maier et al (US Patent Application No. 10/620487, Date of filing July 16, 2003).

Reply to applicants' arguments as they relate to rejection of claims 18 and 19 under 35 USC § 103

At pages 18-19 of remarks, Applicants essentially argue that “Two strategies may be considered for expression of IdhA linked to a GAPDH promoter: one is by use of multicopy plasmid, and the other is insertion into the genome. It is submitted that one of ordinary skill in the art would expect that the use of multicopy plasmid should realize higher expression level than that by insertion into a genome, by virtue of having multiple copies available for transcription and subsequent translation, and therefore would employ this method rather than the claimed genomic integration”. Such is not persuasive.

Claims 19 which depends from claim 18 does not place any limitation on higher expression level of the NADH-dependent D-lactate dehydrogenase obtained from *E. coli* under the control of the glyceraldehyde-3-phosphate dehydrogenase gene obtained from *E. coli*.

Accordingly, if the constitutive GAPDH promoter of the *gapA* gene drives expression of the *yfiK* gene product integrated into a genome in transformant *E. coli*, there is no reason why the GAPDH promoter controlling gene expression in a vector inserted into a genome could not be expected to regulate gene expression in a multicopy plasmid vector as easily as in an integrated vector, as both vectors are useful to express a target protein of interest. The type of gene delivered is irrelevant to control sequence used as promoter.

New Grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 41-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by amendment of the claims in the response filed 12-23-2009.**

Claim 7 is indefinite in the recitation of “an NADH-dependent D-lactate dehydrogenase obtained from *Escherichia coli* and inherent in the microorganism”. The broad genus of claimed microorganisms is very diverse including viruses, bacteria, fungi, plants, animals and others. As the NADH-dependent D-lactate dehydrogenase is obtained from *Escherichia coli*, it is unclear how LdhA is simultaneously inherently present in any microorganism and obtained from *E. coli* other than *E. Coli*. Is NADH-dependent D-lactate dehydrogenase inherently present in any microorganism? Thus the metes and bounds are not clearly set forth.

Claims 41-45 are indefinite insofar as they depend from claim 7.

Claims objection

Claims 7, 15, 18 and 22 are objected to because of the following informalities. In each of these claims the indefinite article “a” and not “an” should precede the abbreviation “NADH”.

Appropriate correction is required

References made of record in a PTO-892 Form to complete the record

Nielsen et al., Applied Microbiology and Biotechnology, 2001 pp.:263–283.

Conclusion

Claims 7, 15, 16, 18, 19 and 41-45 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633